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ORIGINAL ARTICLE

Reformulation of a codeine phosphate liquid controlled-release product

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Abstract

Background: Ion-exchange resins have been successfully used to create drug formulations providing controlled drug release that are easy to swallow, are sufficiently stable, and have good taste-masking characteristics. The objective of the present study was to replace the ion-exchange resin in a proven delayed release codeine preparation with a new resin able to provide the beneficial properties of the original formulations without the need for Eudragit coating to comply with modern manufacturing regulations. *Methods*: Nine cationic exchangers with different particle meshes, form, and pore structures were optimally loaded with codeine and their respective in vitro codeine release profiles were compared using the USP XXIII paddle method. *Results*: The most favorable release profiles were obtained with Amberlite IR 69 F and with Dowex 50 × 8–100. The former was used to prepare the formulated drug–resin complexes as it was available in a pharmaceutically pure form. Both, the cough syrup and concentrate formulations exhibited drug release profiles equivalent to the nonformulated drug–resin complex. These profiles as well as initial free codeine levels, the purity, and the identity were moreover maintained for a storage period of at least 6 months. *Conclusion*: The in vitro dissolution profiles demonstrated that the use of ion exchanger is most suitable for the development of sustained release codeine formulations.

Key words: *Amberlite IRP 69 F; cationic exchanger; codeine; stability*

Introduction

Children, older persons, and disabled or incapacitated patients often experience discomfort when swallowing drugs in tablet or capsule form. This problem, which is exacerbated when the administered drug has a short half-time and must be taken frequently, can reduce therapy compliance. Drugs in liquid suspension form are more easily swallowed but, if poorly water soluble, may form an insoluble sediment during storage which can also interfere with correct dosing. Liquid formulations also have poor taste-masking characteristics.

Generally, controlled-release formulations enhance patient compliance by reducing the frequency of drug administration. Liquid controlled-release formulations are moreover easy to swallow; some of them provide good taste masking and avoid significant drug loss during storage[1–3]. Of the many liquid controlled-release methods available, those using ion exchange have been most widely used because their key properties (particle form and size, pore structure, degree of cross-linkage, water insolubility, and ionizable functional group) can be readily controlled[4–6]. Ion-exchange-based methods also provide effective taste masking[7–9].

The most commonly used resins are strong acid resins bearing sulfonic acid groups (Amberlite IR-100, Dowex-30). Although weak acid resins with carboxylic acid groups like Wolfatit P and Amberlite IR-1 are physiologically more compatible, these cannot be used for long-acting formulations unless the surface of the beads is coated with a barrier layer, for example, by polymerization of α-cyanoacrylate monomers[10]. Bifunctional or polyfunctional ion-exchange resin (Lewatit CNS) contains two or more fixed ionic groups[11]. Copolymeric resins prepared

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from different vinyl monomers offer the advantages of high thermal and chemical stability. The most important resins of this type are cross-linked polystyrenes with sulfonic acid groups introduced after polymerization by treatment with concentrated sulfuric acid or chlorosulfonic acid, that is, Amberlite IR-120, Dowex-50, Nalcite HCR, Permutit Q, Duolite C-20 and C-25, and Lewatit S-100[11].

The process of drug binding to and release from a sulfonic acid resin is depicted in Figure 1. The drug–resin complex is created by exchanging the protons of the sulfonic acid groups with the drug cation (Figure 1a). Following ingestion of the complex, the drug is slowly released in the stomach by exchange with protons in the gastrointestinal fluid (Figure 1b) and subsequently released in the intestine by exchange with Na^+ and K^+ ions (Figure 1c)[12]. The cation concentrations prevailing in the stomach and intestine and thus the actual drug release profile are modulated by food consumption. Drug release kinetics are also influenced by temperature.

Codeine, an opiate drug with both analgesic and cough suppressant activities widely used in many medications, has a plasma half-time of 2.9 ± 0.7 hours[13]. To avoid patient compliance problems associated with solid and liquid formulations, the pharmaceutical industry has developed sustained liquid controlled-release codeine formulations using ion-exchange resins[14], such as Codipertussin® Cough Syrup and Codipertussin® Concentrate Drops. These products, which contain a codeine–resin complex coated with Eudragit RL 100, successfully provide a prolonged codeine plasma profile and also exhibit a high degree of stability and have good taste-masking characteristics. The resin coating process, which involves the evaporative removal of organic solvents such as methylene chloride, is however time consuming and has been further complicated by the introduction of stringent environmental regulations controlling the use of organic solvents.

The objective of the present study was to simplify the manufacture of Codipertussin® syrup and concentrate by identifying an alternative ion-exchange resin able to provide the beneficial properties of the original formulations without coating.

Material and methods

Materials

Codeine phosphate was purchased from Hauser, Klagenfurt, Austria. Nine cationic exchangers were used as model resins (Sigma, Vienna, Austria; Röhm & Haas, Darmstadt, Germany). All other chemicals were purchased from Merck, Darmstadt, Germany, unless otherwise indicated. The resins (Table 1) were pretreated with 2 N ammonia, 2 N hydrochloric acid, or with 1 N hydrochloric acid. The liquid carrier used for the resins (Table 2) consisted mainly of glucose syrup and saccharose (Herba, Graz, Austria), potassium sorbate, methyl-4-hydroxybenzoate and propyl-4-hydroxybenzoate (Herba), citric acid monohydrate and Keltrol CG-RD (Jungbunzlauer, Wulzeshofen, Austria), bitter orange oil (Paul Kaders GmbH, Hamburg, Germany), passion fruit concentrate (Bayernwald, Hengersberg, Germany), β-carotene (Hoffmann La Roche, Basel, Switzerland), and ethanol (Herba). For in vitro release studies, 0.1 N hydrochloric acid and tris-phosphate-dodecahydrate buffer were used as gastric and intestinal dissolution media, respectively. The Aluspher 100 RP select B, Li Chro Cart 250-4 HPLC column was purchased from Merck. The mobile phase contained methanol (HPLC grade, Merck), acetonitrile (HPLC grade, Merck), diethylamine (HPLC grade, Merck), and distilled water.

Resin pretreatment

With the exception of Amberlite IR 69 F, which is a pharmaceutically pure resin, all cationic exchangers used in the study were pretreated prior to codeine phosphate loading to remove low-molecular-weight polymer residues. The pretreatment was carried out according to the manufacturer's specification. Each resin (100 g) was washed three times with 200 mL water, heated with 100 mL of 2 N ammonia and 100 mL of 2 N hydrochloric acid before charging with 200 mL of 1 N hydrochloric acid. The treated resins were then neutralized by washing with water and dried for 5 days at 105°C in a vacuum oven (Heraeus Type VT, 5042 EK, pump, Hanau, Germany: Vacuubrand Type RC5). The surface morphology and shape of Amberlite IR 69 F and purified Dowex-50W were examined by scanning electron microscopy (SEM) and the results recorded with a Philips XL 30 ESEM (Eindhoven, The Netherlands).

Preparation and characterization of the drug–resin complex

The drug–resin complexes were prepared by shaking the pretreated resins for 10–12 hours in an aqueous solution of codeine phosphate at different drug:resin ratios using a Bühler Type B1 shaking device (Bühler, Tübingen, Germany) and oven drying at 30°C. The drug contents of the complexes were determined by high-performance liquid chromatography (HPLC) and UV spectroscopy (284 nm) following drug release. Unbound codeine was determined from the absorption of the filtrate via UV spectroscopy. For the HPLC method, 100 mg of loaded resin was mixed with 80 mL $MeOH/NH_3$ in a 100 mL flask, ultrasonicated for 15 minutes, shaken for 15 minutes, and then subjected to ultrasonication for 60 minutes. A further 20 mL of $MeOH/NH_3$ was then

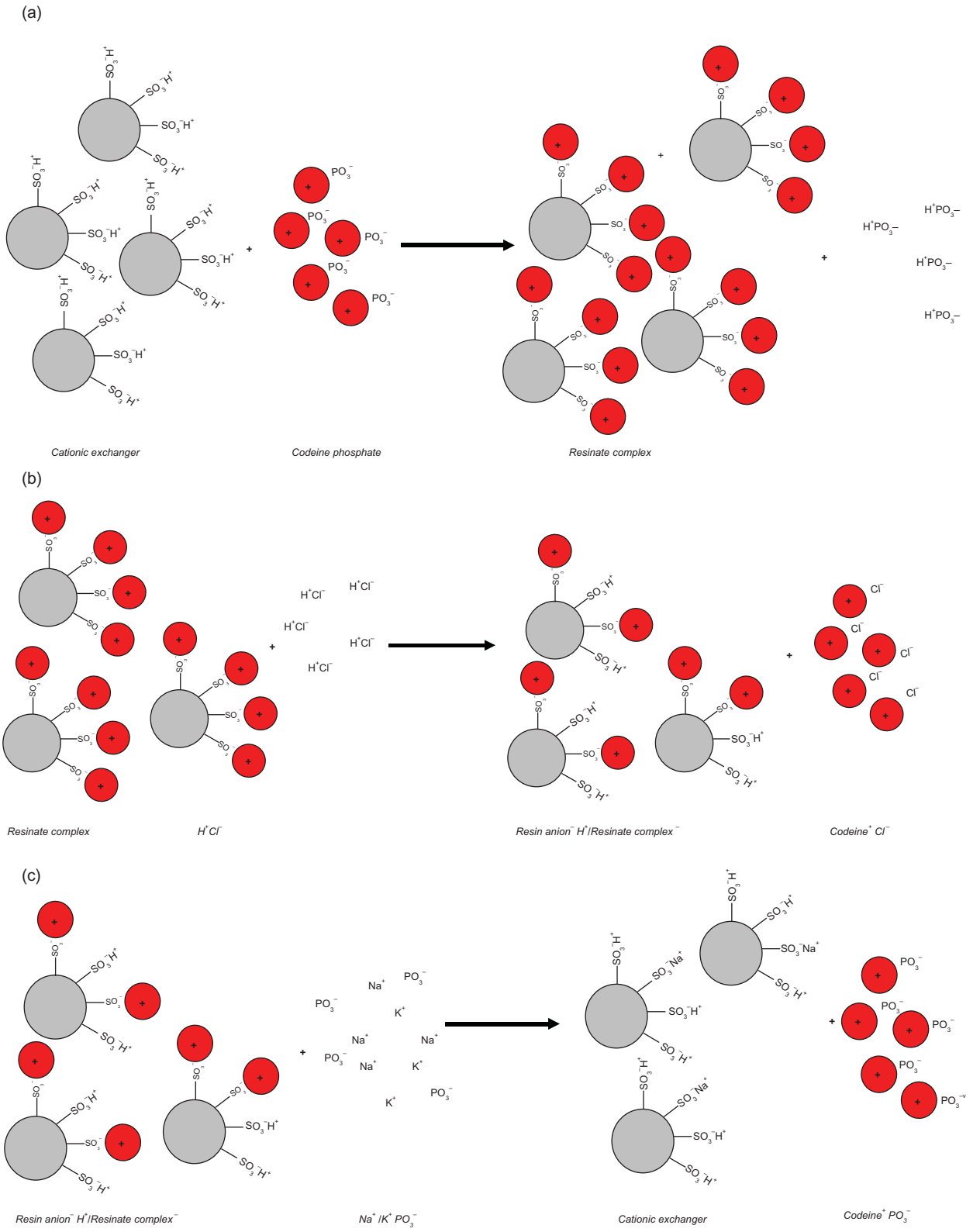

Figure 1. Schematic representation of the cationic exchange process. (a) The drug ions are loaded onto the resin by exchange with the sulfonic acid group protons. (b) After ingestion of the complex, the cationic exchange process is partially reversed in the stomach, resulting in the release of about 50% of the adsorbed drug after 2 hours, and (c) The cationic exchange process is completed in the intestine, where the drug exchanges with the Na^+/K^+ ions of the intestinal fluid.

Table 1. Cationic exchangers used in the study and values for key parameters.

Ion exchanger	Moisture content (%)	Mesh	Cross-linkage (%)
Dowex-50W 50x2-100	74–82	50–100	2
Dowex-50W 50x2-200	74–82	100–200	2
Dowex-50W 50x4-100	64–72	50–100	4
Dowex-50W 50x4-400	64–72	200–400	4
Dowex-50W 50x8-100	50–56	50–100	8
Dowex-50W 50x8-200	50–58	100–200	8
Dowex-50W 50x8-400	50–58	200–400	8
Amberlite IR120 Plus	45	16–50	8
Amberlite IR 69 F	44–48	16–50	8

Table 2. Components of the liquid carrier of the cough syrup and the cough concentrate for 1 L of syrup.

Component	Mass (g)
Potassium sorbate	1.62
Methyl-4-hydroxybenzoate	0.79
Propyl-4-hydroxybenzoate	0.68
Saccharose	282.50
Glucose syrup	282.50
Citric acid monohydrate	3.35
Bitter orange oil	0.037
Passion fruit concentrate	27.88
β-Carotene	0.07
Keltrol CG-RD	6.95
Ethanol	4.09
Purified water	572.40

added and the samples were shaken again and then centrifuged for 10 minutes at $2,300 \times g$ (Eppendorf Centrifuge 5415C, Hamburg, Germany). The supernatant was then diluted 1:5 with HPLC mobile phase and the concentration of released codeine was determined by HPLC as described below (Analysis).

The UV method for codeine determination was applied after a 24 hours of drug release using the United States Pharmacopoeia (USP) XXIII apparatus 2 method <724>. To ensure that complete release had occurred, the drug–resin complex was ultrasonicated for 20 minutes and again measured spectroscopically.

In vitro release studies

The kinetics of in vitro codeine release from the drug–resin complexes were determined using the USP XXIII apparatus 2 method <724>. The apparatus used (Pharma Test Type PTWS III C) was operated at a release temperature of 37 ± 0.5°C and a stirring speed of 100 rpm. Each of the six vessels was initially filled with 750 mL of 0.1 N hydrochloric acid. After 2 hours, the pH was raised from 1.2 to 6.8 by adding 250 mL of tris-phosphate-dodecahydrate buffer. For each resin 1 g of the formulation was filled into the six vessels. Samples of 10 mL were taken at time zero to determine the initial concentration and subsequently at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours, centrifuged for 10 minutes at $21,000 \times g$, and the codeine content was determined by HPLC and UV analysis as described below (Analysis). The withdrawn sample volume was replaced by fresh medium.

Statistical analysis was performed with SigmaPlot Version 11 (SysStat) using a one-way ANOVA method without repeated measurements.

Analysis

Codeine concentrations were determined by HPLC and UV spectroscopy.

HPLC analysis was carried out using a Waters system (Autosampler 717 PLUS, En Yvelines Cedex, France, Waters 510 Pump A, En Yvelines Cedex, France). An analytical column (Alusphere RP select B, Li Chro Cart 250-4, 5 μm particle size, 250 mm length, and 4 mm internal diameter, Merck) was used at 30°C with a flow rate of 0.8 mL/min and an injection volume of 20 μL. The mobile phase consisted of methanol (155 mL), distilled water (707 mL), acetonitrile (68 mL), and diethylamine (0.1 mL). Each sample (200 μL) was diluted with 600 μL of a solution consisting of 10 mL MeOH/NH_3 and 50 mL mobile phase. The UV detector (Waters 490 E, En Yvelines Cedex, France) was set at 284 nm. UV analysis was carried out using a Shimadzu UV-160 A spectrophotometer (Duisburg, Germany). A high degree of correspondence was observed between codeine concentrations determined by HPLC and those obtained by the UV method.

Preparation of the liquid drug formulation

About 1 L of syrup was prepared in the following way: potassium sorbate (1.62 g) was dissolved in 23.32 g purified water. *p*-Hydroxybenzoate propyl ester (0.68 g) was dissolved in 4 g ethanol using a magnetic stirrer and 0.037 g bitter orange oil was added to this solution and stirred for 5 minutes. β-Carotene (0.07 g) was dissolved in 23.32 g water at 40°C. Citric acid, saccharose, and *p*-hydroxybenzoate methyl ester were then added to the remaining water and stirred for 20 minutes. The glucose syrup was meanwhile preheated in the oven to 80°C and added to the saccharose solution. This was then homogenized before adding the potassium sorbate solution and cooling the mixture to 60°C. The ethanolic solution of *p*-hydroxybenzoate propyl ester was then added, followed by the bitter orange oil solution and the passion fruit concentrate. The drug–resin complex was added at this stage. The preparation was completed by the addition of β-carotene and Keltrol CG-RD (xanthan gum). Finally, the mixture was homogenized and adjusted to a pH of 3.3–3.6 using a 30% NaOH solution (all of the syrup constituents and the masses used are

summarized in Table 2). The viscosity of the mixture was set to approximately 1200 mPa/s according to the manufacturer's description of Keltrol. The resin–drug was incorporated into the liquid in two different concentrations, that is, the 'Cough Syrup' containing 230 mg codeine base/100 mL and the 'Cough Concentrate' containing 697 mg codeine base/100 mL.

The drug release profiles of the resin–drug formulations were measured by the apparatus 2 method <724> according to United States Pharmacopoeia XXIII.

Results and discussion

Selection of optimum ion-exchange resin

The nine cationic exchangers investigated in the study and the respective values for key parameters are listed in Table 1. The resinates showed differences in their size (mesh), degree of cross-linking, and their moisture content. All ion exchangers had a smooth and nonporous surface structure. However, the SEM images of the ion exchangers revealed differences in the shape. Most strikingly, whereas Dowex-50W was spherical, Amberlite IR 69 F exhibited an irregular shape (Figure 2). Small and fine particles had a greater surface area and a less internal volume. Thus, with decreasing particle size codeine was released faster. The surface structure as well as the shape did not influence the release profile of the drug. Regarding the cross-linkage, higher cross-linked resins displayed a more retarded release of codeine in comparison with lower cross-linked resins as demonstrated in Figure 3. The moisture content, which is also an important key parameter, decreased with increasing cross-linkage. Thus, ion exchangers with low cross-linkage showed a higher ability to hold water inside the particle and released the drug faster.

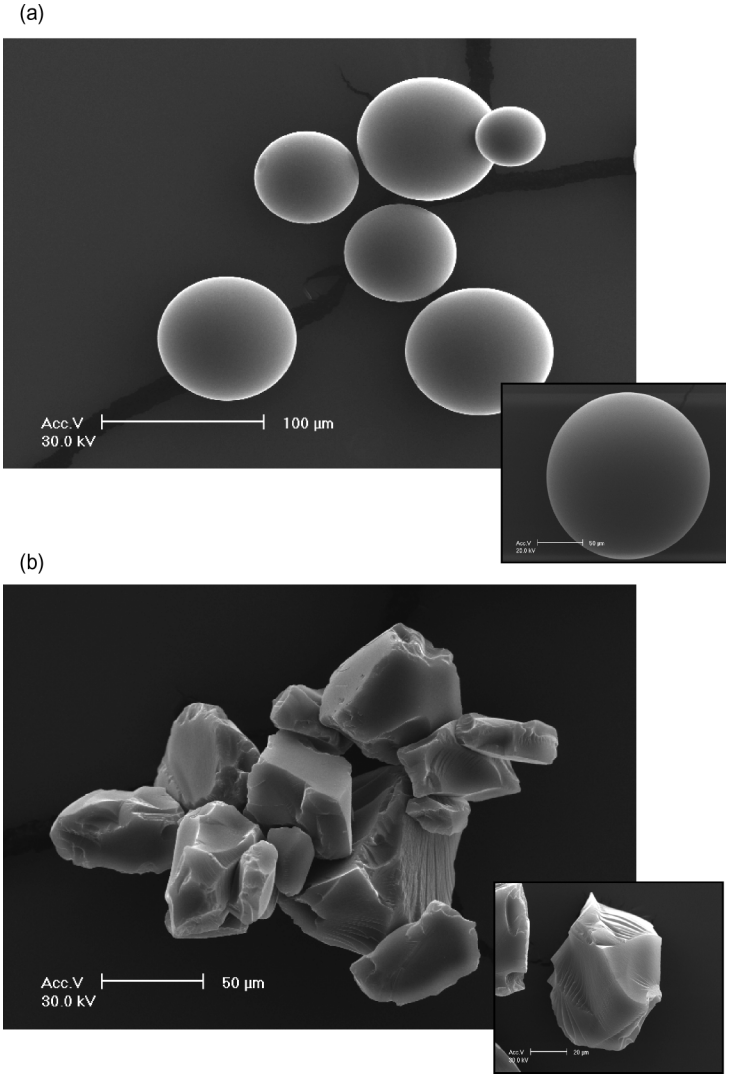

Figure 2. Scanning electron microscopy images: surface of Dowex-50W (a) and Amberlite IR 69 F (b).

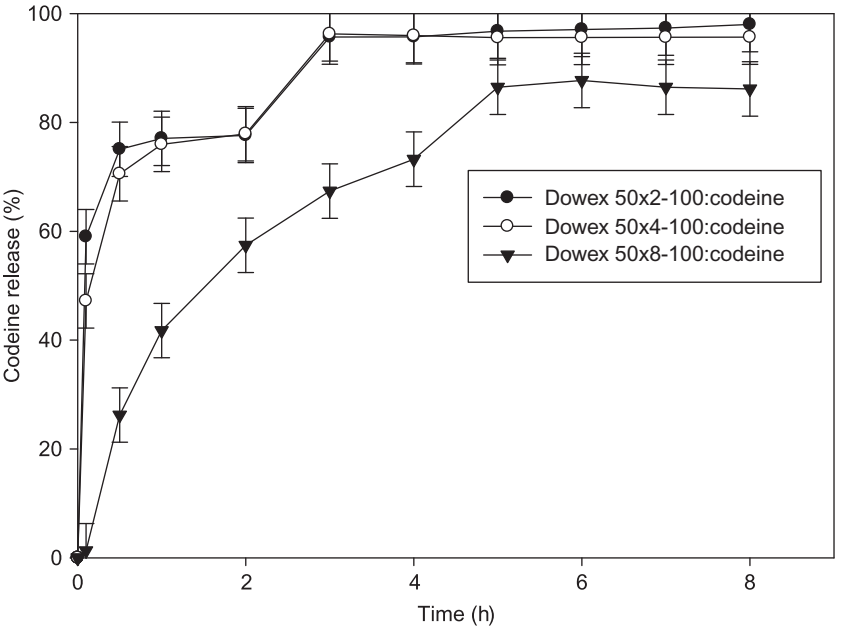

Figure 3. In vitro release curves for the codeine–resin complexes according to their cross-linkage. Mean ± SD values of six vessels are shown.

Some of the codeine content determinations were analyzed by UV spectroscopy only; other drug quantifications were performed by HPLC. A comparison of both methods was applied during the analytical method validation as UV spectroscopy was found to be less specific than HPLC.

Following pretreatment, drug–resin complexes were prepared using a range of drug:resin ratios (0.2:1–2:1) to identify the minimum amount of resin needed to achieve at least 95% codeine loading. Ratios of 2:1 and 1:1 resulted in loading efficiencies ranging from 75% to 90%. A ratio of 0.5:1 produced loading of 95% for all resins. In vitro codeine release was then measured as a function of time for drug–resin complexes prepared using this drug:resin ratio. In general, the use of lower ratios showed highly variable release profiles and, therefore, was not further investigated. The profiles of the in vitro release curves obtained varied markedly according to the resin used. The most favorable release profiles, which were defined to have an initial dose below 20% and to reach a complete release of >90% drug after 7 hours, were obtained with Dowex 50x8-100 and Amberlite IR 69 F (Figure 4). Interestingly, the degree of resin cross-linkage (Table 1) was found to influence the kinetics of drug release. Thus, as shown in Figure 3, a more favorable codeine release profile was obtained with Dowex 50x8 (8%) than with Dowex 50x4 and Dowex 50x2 resins (4% and 2%, respectively). These results demonstrated, as already mentioned above, that the cross-linkage of the resin will mainly influence the diffusion coefficient of ions within the polymer meshwork and the higher the cross-linkage, the more retarded the ion exchange.

Although Amberlite IR 69 F and Dowex 50x8-100 exhibited equivalent in vitro drug release properties, only the former was available in a pharmaceutically pure form. The different meshes of the ion exchangers used in the experiments (16–50, 50–100, respectively) did not influence the drug release within 8 hours. However, Amberlite IR 69 F was selected for liquid formulation experiments to minimize further preformulation work and consequently in vivo toxicity studies prior to our pharmacokinetic study[15].

Characterization of liquid-formulated codeine-loaded Amberlite IR 69 F

Two liquid formulations of codeine-loaded Amberlite IR 69 F containing two different codeine concentrations were prepared by formulation in syrup (Materials and Methods). The 'Cough Syrup' contained 230 mg codeine base/100 mL, whereas the 'Cough Concentrate' contained 697 mg codeine base/100 mL. The viscosity of the liquid carrier was 0.16 Pa s and was easy to dose to enhance patient compliance.

The in vitro codeine release profiles were determined for both formulations with the USP XXIII apparatus 2 method as described above. In each case, the liberation curves obtained demonstrated gradual codeine release during the 8-hour measurement period equivalent observed with the nonformulated drug–resin complex (data not shown).

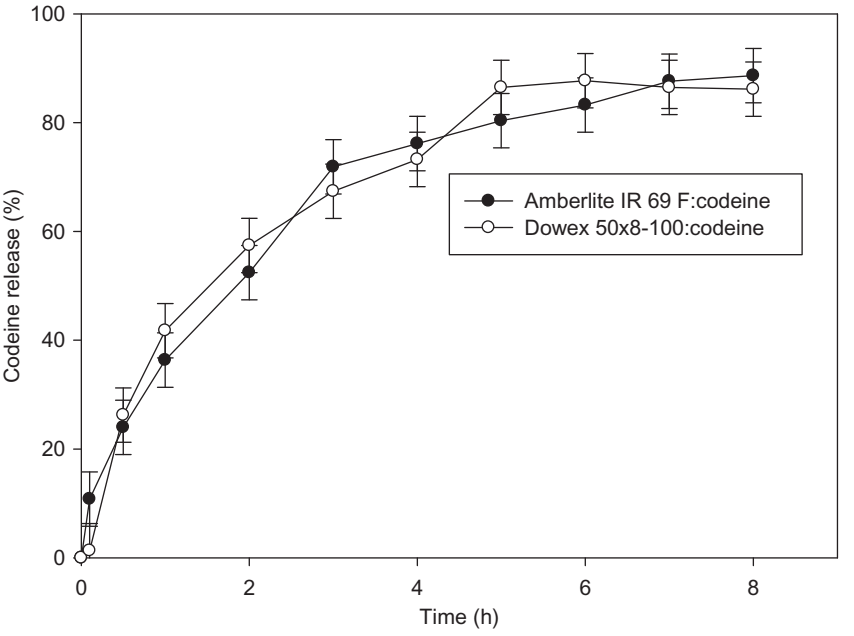

Figure 4. In vitro release curves for the two codeine–resin complexes exhibiting the most favorable drug release profiles. Mean ± SD values of six vessels are shown.

Stability of liquid-formulated codeine-loaded Amberlite IR 69 F

The stability of both dosage forms was investigated using batches prepared for this purpose. Samples were taken immediately, then 1 month, and 6 months after preparation for the determination of (i) the initial codeine concentrations, (ii) chromatographic purity and identity, and (iii) the drug release profile. As shown in Table 3, the amount of free codeine did not change significantly during storage. Approximately, 16–25% and 5–7%, respectively, of codeine was present in the liquid in an unbound form at 1 and 6 months. This can be explained because of the solubility of the drug. The concentrate had a three times higher drug concentration in contrast to the syrup.

The identity and purity tests carried out by thin layer chromatography (data not shown) demonstrated the absence of degradation products and an adequate level of microbiological stability. The in vitro release curves as well as the one-way ANOVA results obtained for the cough syrup (Figure 5) and for the cough concentrate (Figure 6) showed that the drug release profiles of both remained essentially unaltered by storage within 1 and 6 months. Comparing the initial drug release, a slight degree in drug loss was found between 0 and 6 months. Organoleptic tests, moreover, detected no differences in taste, consistency, and appearance. Therefore, the objective of the present study, to simplify the manufacture of Codipertussin® syrup and concentrate by identifying an alternative ion-exchange resin able to provide the beneficial properties of the original formulations without coating, was fulfilled.

Conclusions

It was shown that among nine resins, Amberlite IR 69 F was most suitable as a cationic exchanger for the loading with codeine phosphate and incorporation into a liquid carrier. The drug–resin complexes were prepared by shaking the (pretreated) resins in aqueous drug solutions at different drug:resin ratios. The ratio of 0.5:1 produced loading of 95% and provided the best in vitro codeine release profile with an initial dose below 20% and a complete release of >90% drug after 7 hours. The degree of resin cross-linkage as well as the particle size was found to influence the kinetics of the drug. After incorporation of two different concentrations of the

Table 3. Comparison of the free codeine concentrations in the cough syrup and in the cough concentrate during 6 months storage.

Formulation	Codeine concentration after 1 month (%)	Codeine concentration after 2 months (%)	Codeine concentration after 3 months (%)	Codeine concentration after 6 months (%)
Cough syrup	16.13	16.35	21.09	25.38
Cough concentrate	5.23	3.27	5.75	7.46

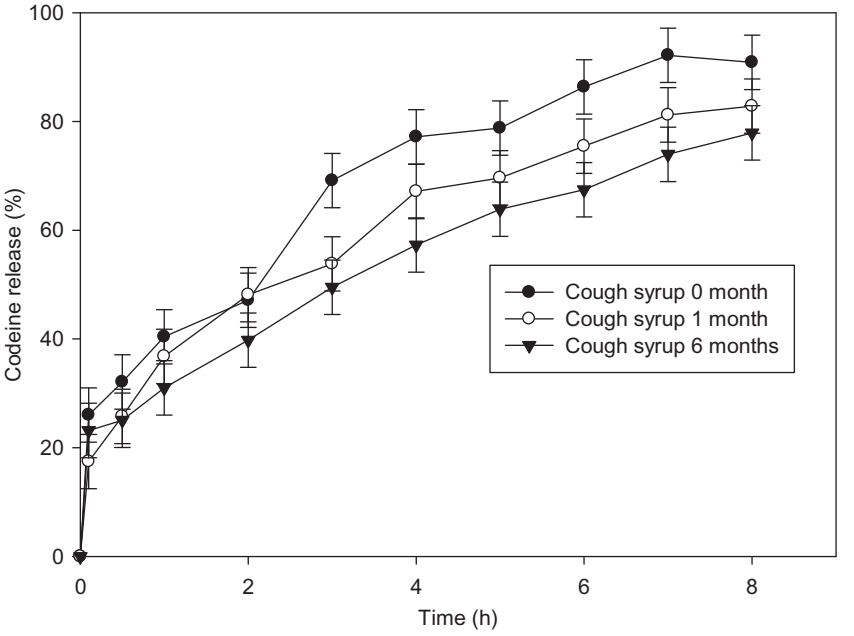

Figure 5. In vitro release profiles for the cough syrup after 0 month, 1 month, and 6 months of storage. Mean ± SD values of six vessels are shown. No statistically significant differences were found between 1- and 6-month storage time (ANOVA; $P > 0.05$).

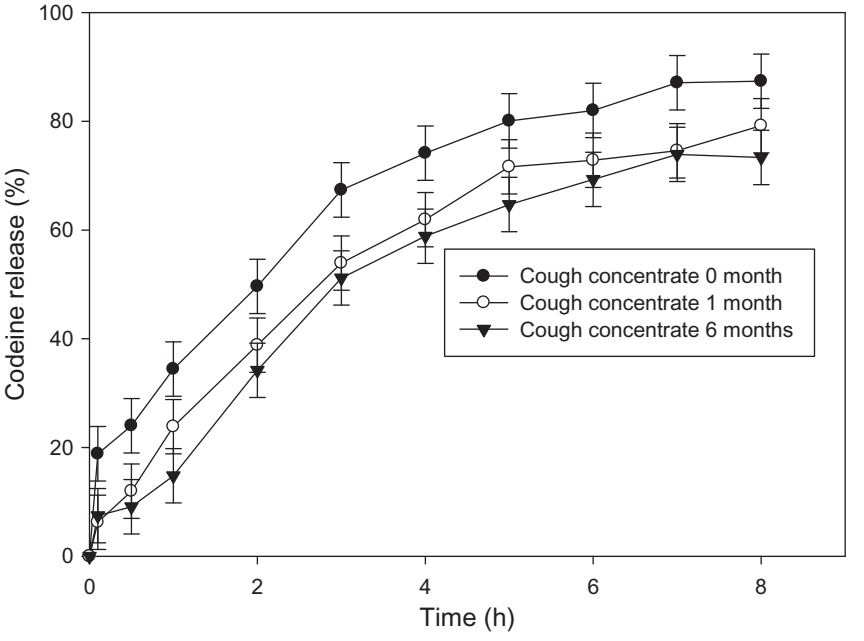

Figure 6. Comparison of the in vitro release profiles of the cough concentrate after 0 month, 1 month, and 6 months of storage. Mean ± SD values of six vessels are shown. No statistically significant differences were found between 1- and 6-month storage time (ANOVA; $P > 0.05$).

drug–resin complex into a liquid carrier (i.e., syrup and concentrate) the amounts of unbounded codeine showed no significant differences. The in vitro release kinetics after storage for 6 months demonstrated a slight drug loss between the initial drug release analysis and 6 months. Our results demonstrate the feasibility of preparing liquid controlled-release formulations of codeine providing delayed drug release using a process that is both simpler than that used to prepare the analogous Codipertussin® products and that importantly complies

with modern environmental regulations. The favorable release kinetics reported here were also observed in a pharmacokinetic study in human volunteers that is described in an accompanying manuscript[15].

Acknowledgments

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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